II. REMARKS

Preliminary Remarks

Claims 28-31 and 40-50 are pending of which claims 28 and 44 are independent. Claim 28 is amended to be directed to a method of treating a disease selected from the group consisting of arthritis, tendonitis, phlebitis, psoriasis, acne, eczema, dermatitis, and wounds in a human or animal, the method comprising administering to said human or animal a pharmaceutically effective amount of a fish serine protease. Support for the claim amendments can be found in the specification and claims as originally filed (see, for example, page 2, paragraph beginning on line 21 and Examples 4-13). Therefore, the applicants believe that no new matter has been added as a result of these amendments.

The drawings were objected to for allegedly being visually unclear. The applicant submits herewith Figures 1-4.

Claim 43 was objected to for missing the word "or". This claim is amended to incorporate this word and the applicant respectfully requests withdrawal of this objection.

This response is timely filed within the shortened statutory period for response. Thus, the applicant believes that no fee is due. The applicant respectfully requests reconsideration and allowance of the present application.

Patentability Remarks

Rejections under 35 U.S.C. §112, first paragraph –

Claims 43 and 48 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. The applicant respectfully traverses in view of the preceding amendments and succeeding remarks.

Trypsin sequences from various species are very well known. To illustrate this fact, the applicant encloses a copy of a review paper by Leiros *et al.* (*Extremophiles* **3**, 205 – 219, 1999) in which a comparison of the amino acid sequence of trypsin from a variety of sources is made. In figure 2 on page 209, Leiros *et al.* provide percentage sequence identity (*i.e.*, homology) of various trypsins. Trypsins from cold-adapted organisms (Salmon (AST-II and AST), antarctic fish (AFT), Atlantic cod (CT-I and CT-X) and putterfish (PFT)) have a sequence homology of 78-97%, whereas the homology with respect to trypsin from various vertebrates is in the range of 55-68% (top right quadrant of Figure 2), which in turn is similar

to the sequence homology of less than 70% with the multifunctional krill enzyme (page 1, paragraph beginning on line 29).

It should also be noted that on page 12, paragraph beginning on line 21, of the present application, it is shown that 13 out of the 225 amino acid positions in Atlantic cod are polymorphic, and thus giving rise to multiple isoforms of the Atlantic cod trypsins. This number corresponds to about 6% of the amino acid residues in Atlantic cod trypsin. As a consequence, the applicant maintains that it would not constitute undue experimentation of a person of ordinary skill in the art to produce the claimed variants, especially in light of the established natural variability of the cod trypsins. Furthermore, the claimed range of sequence homology corresponds approximately to the range of of polymorphism which is expected to occur in nature without significantly affect the functional characteristics (*i.e.*, activity) of the claimed trypsins.

Furthermore, the applicant notes that claims 43 and 48, which are dependent on claim 29 and 45, are restricted to trypsins. Thus, the claimed sequences must fulfill the stated sequence homology *and* they must have the same catalytic properties as trypsin. Therefore, the applicant respectfully submits that claims 43 and 48 fully comply with the enablement requirement under 35 U.S.C. §112, first paragraph, and respectfully requests withdrawal of this rejection.

Claims 28-31 and 40-42 were rejected under 35 U.S.C. §112, first paragraph, as allegedly not providing enablement for treating all diseases and preventing certain skin conditions. The applicant respectfully traverses in view of the preceding amendments and succeeding remarks.

As amended, claims 28-31 and 40-42 are directed to a method of treating a disease selected from the group consisting of arthritis, tendonitis, phlebitis, psoriasis, acne, eczema, dermatitis, and wounds in a human or animal, the method comprising administering to said human or animal a pharmaceutically effective amount of a fish serine protease. The applicant respectfully submit that claims 28-31 and 40-42 are fully enabled by the specification as filed and respectfully requests withdrawal of this rejection.

Rejection under 35 U.S.C. §103(a) –

Claims 28-31, 40-42, and 44-50 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over de Faire *et al.* (U.S. Pat. No. 5,958,406). The applicant respectfully traverse in view of the preceding amendments and succeeding remarks.

The examiner alleges that de Faire *et al.* disclose a method for treating skin conditions such as acne and eczema with a multifunctional enzyme exhibiting at least one of chymotrypsin, trypsin, collagenase or elastase activity. It should, however, be noted that the only enzyme that is actually disclosed in de Faire *et al.* is the multifunctional krill enzyme.

Furthermore, with respect to the examiner's allegation that a prediction of the effect of amino acid substitution on protein structure or function is extremely complex, and therefore it can be difficult to use sequence data from one protein to predict functional aspects of the protein itself or other proteins with similar sequence, it should be noted that cod derived trypsin and chymotrypsin as disclosed in the present application have less than 70% homology with the krill derived multifunctional enzyme (page 1, paragraph beginning on line 29), which is comparable to the sequence homology with respect to mammalian trypsins, as discussed in the above. Therefore the statement made in by de Faire *et al.* in column 1, lines 18-20, that "the enzymes that are substantially structurally similar to the krill-derived multifunctional enzyme have the same utility as the krill enzyme" would not lead one of ordinary skill in the art to recognize that the serine proteases of present invention would have the same utility as disclosed by de Faire *et al.*, because of their relatively low sequence homology.

In fact, it turns out that the serine proteases of the present invention have unexpected and unforseen advantages over the multifunctional enzyme from krill or other conventional proteases. Thus, as disclosed on page 10, paragraph beginning on line 31, "when a panel of 13 of the most active proteases in this respect were compared for activity towards ... the Atlantic cod trypsin and chymotrypsin were found to be the far most active," and "on the basis of this scoring scheme the Atlantic cod trypsin scored 30 points and the Atlantic cod chymotrypsin scored 29 points, whereas the known krill multifunctional protease scored 16 points."

The physiological effect of the present invention is believed to be due to the activity of the fish serine proteases towards the cleavage or inactivation of cytokines, inflammatory mediators and matrix metalloproteinases (page 10, paragraph beginning on line 11), and their surprising effect over the enzymes disclosed by de Faire *et al.*, is believed to be due to differences in substrate specificity and specific activity. In particular, it is believed that the fish derived serine proteinases have a surprising and unforseen penetrating effect, which may be related to their high activity towards many cell-surface adhesion molecules, which is

markedly higher than *e.g.*, that of krill-derived multifunctional enzyme (page 7, paragraph beginning on line 29).

These increased penetrating effects are believed to underly the activity of the fish serine proteases for treatment of pain, acute inflammation, chronic inflammation, arthritis, inflamed joints, bursitis, osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, septic arthritis, fibromyalgia, systemic lupus erythematosus, phlebitis, and tendonitis (see page 2, paragraph beginning on line 21 and Examples 4-13), which are all activities which the multifunctional enzyme disclosed by de Faire *et al.* does not appear to have.

The applicant submits that (i) a person of ordinary skill in the art would not have been motivated to administer fish serine proteases such as the Atlantic cod serine proteases based on the teachings of de Faire *et al.*; and (ii) that the fish serine proteases from Atlantic cod were in fact found to display unexpected properties of pharmaceutically high activity against certain diseases. It would not have been obvious for one of ordinary skill in the art to use the fish derived proteinases of the present application for treating the above-mentioned diseases, as the disclosure of de Faire *et al.* would not point the skilled person in that direction, *i.e.*, treatment of the above-mentioned diseases. Therefore, the applicant respectfully submits that claims 28-31, 40-42, and 44-50 are not unpatentable over de Faire *et al.* under 35 U.S.C. §103(a) and respectfully request withdrawal of this rejection.

III. CONCLUSION

In view of the foregoing, the applicant believes that the claims are in form for allowance, and hereby respectfully solicit such action. If any point remains in issue which the examiner feels may be best resolved through a personal or telephone interview, the examiner is strongly urged to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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